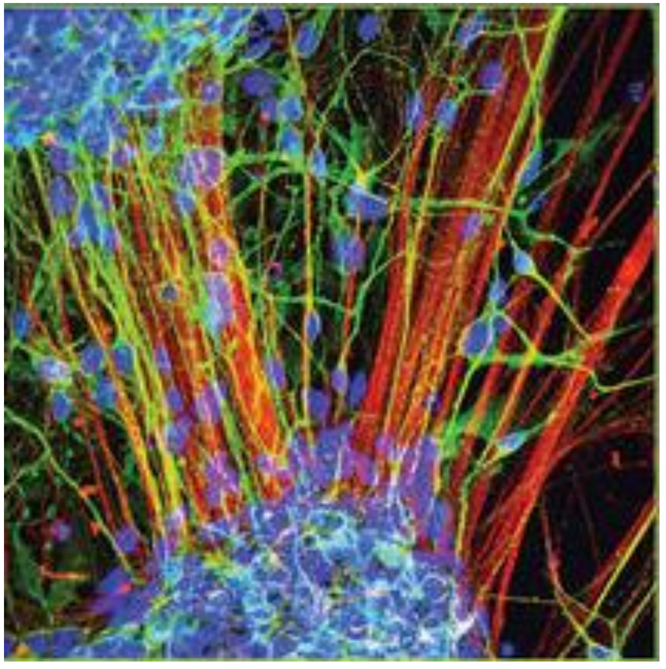
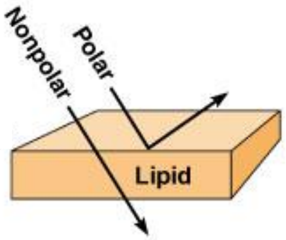


Biol 266 – Cell Biology

UNIT 3
"Membrane structure"

History of biological membranes

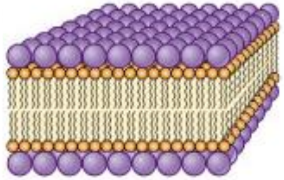
1. Cells must be surrounded by lipids since lipid-soluble substances penetrated cells but polar substances did not.



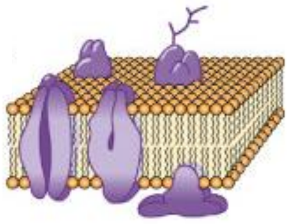
2. Lipids arrange themselves into a layer, called a monolayer.

3. Erythrocyte plasma membrane occupies twice the expected area. Therefore, the membrane is composed of a lipid bilayer.

4. Proteins must account for the selective permeability of membranes. Proposed to coat both sides as a sheet (sandwich model).



5. Some proteins are hydrophobic and must embed in the membrane. The fluid-mosaic model proposes an underlying fluid-like bilayer with a mosaic of proteins embedded within the lipids.

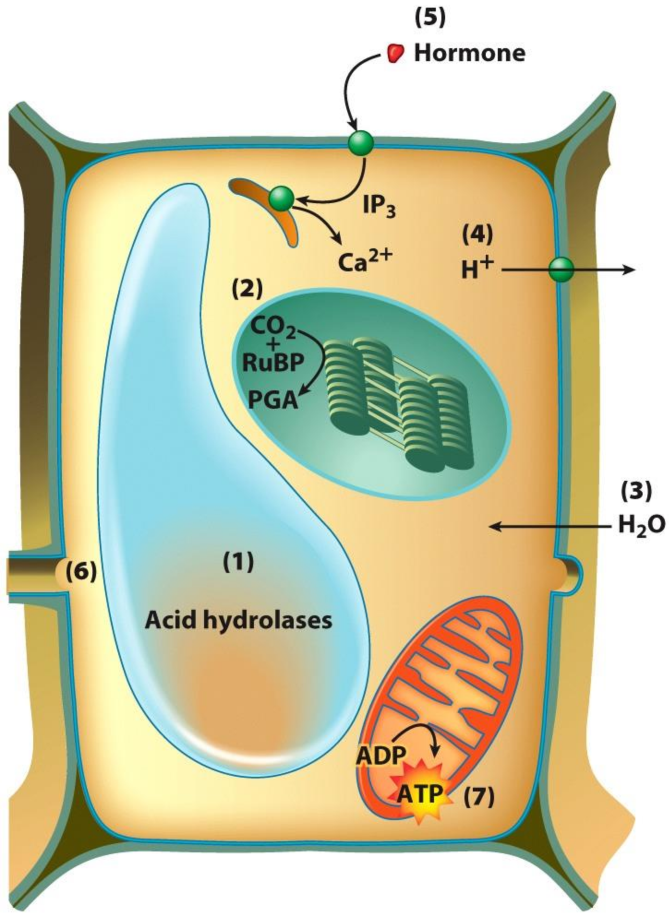


Functions of biological membranes

1. **Compartmentalization** Membranes form continuous sheets that enclose intracellular compartments.

2. **Scaffold for biochemical activities**
   Membranes provide a framework that organizes enzymes for effective interaction.

3. **Selectively permeable barrier**
   Membranes allow regulated exchange of substances between compartments.



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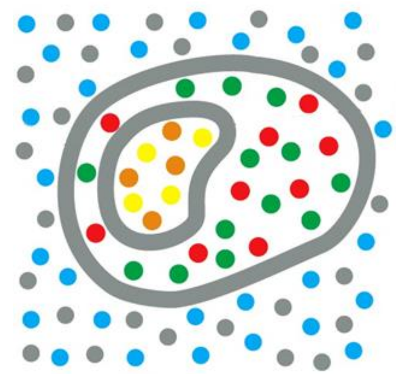


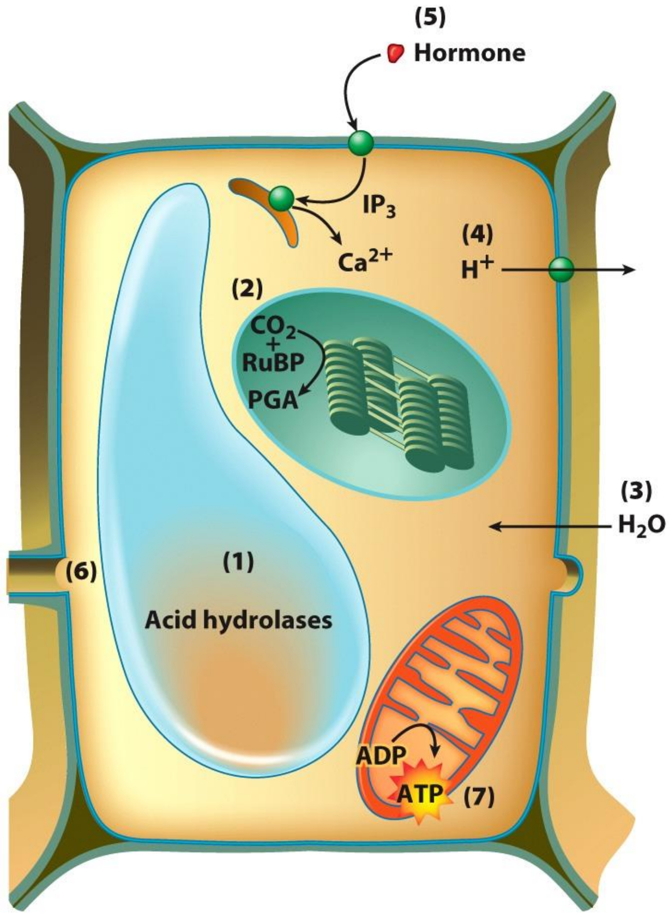
Functions of biological membranes

4. **Transporting solutes**
   Membrane proteins facilitate the movement of substances between compartments.

5. **Responding to external signals**
   Membrane receptors transduce signals from outside the cell in response to specific ligands.

6. **Intercellular interaction**
   Membranes mediate recognition and interaction between adjacent cells.

7. **Energy transduction**
   Membranes transduce photosynthetic energy, convert chemical energy to ATP, and store energy.



Plasma membrane-specific functions

1. Import and export of molecules

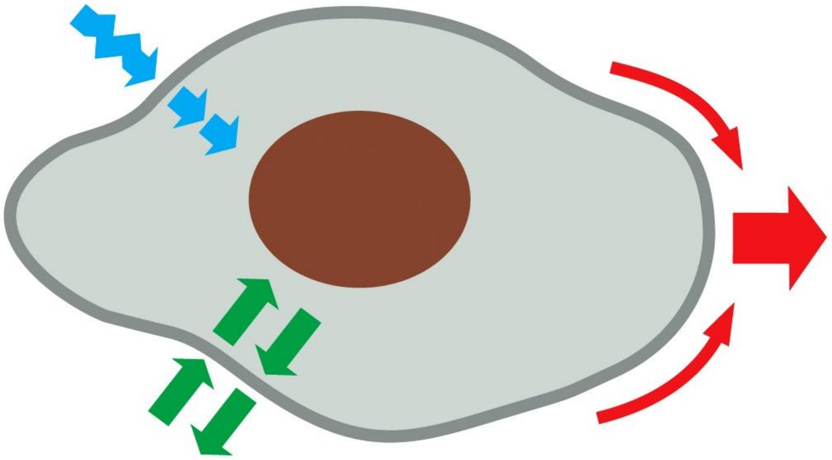
Nutrients pass inward across the plasma membrane, waste products pass outward

2. Receiving information

Some proteins in the plasma membrane act as sensors (receptors) to enable the cell to respond to changes in its environment

3. Capacity for movement and expansion

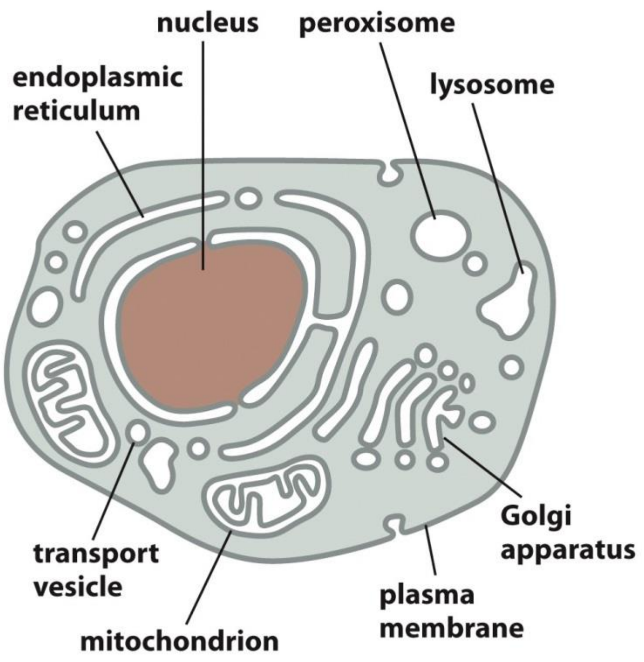
When the cell grows or changes shape, the plasma membrane enlarges its area by addition of new membrane and it can deform without tearing



The membranes that surround the organelles of eukaryotic cells separate one aqueous phase (the cell cytosol) from another (the interior of the organelle). Internal membranes serve as selective barriers between the cell cytosol and the interior of individual organelles.

The membranes of the organelles maintain the characteristic differences in composition between these organelles.

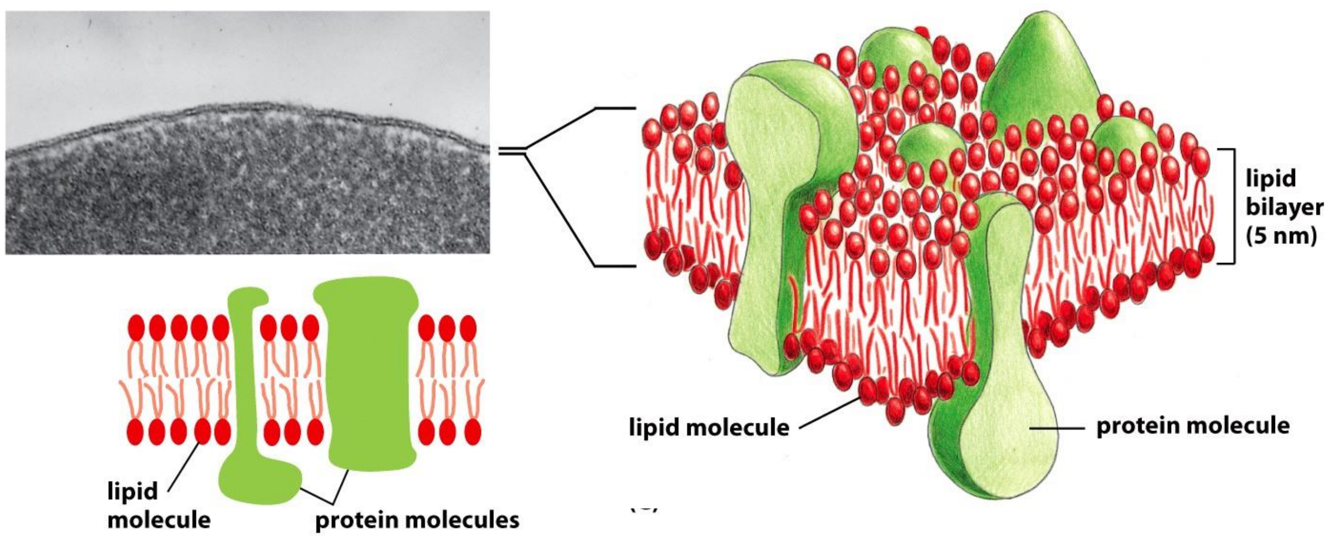
Subtle differences between them, especially differences in the membrane proteins, are largely responsible for giving each organelle its distinct character.



All cell membranes are composed of lipids and proteins and have a common general structure.

The lipid component consists of many millions of lipid molecules arranged in two closely apposed sheets, forming a lipid bilayer, ~5 nm thick.

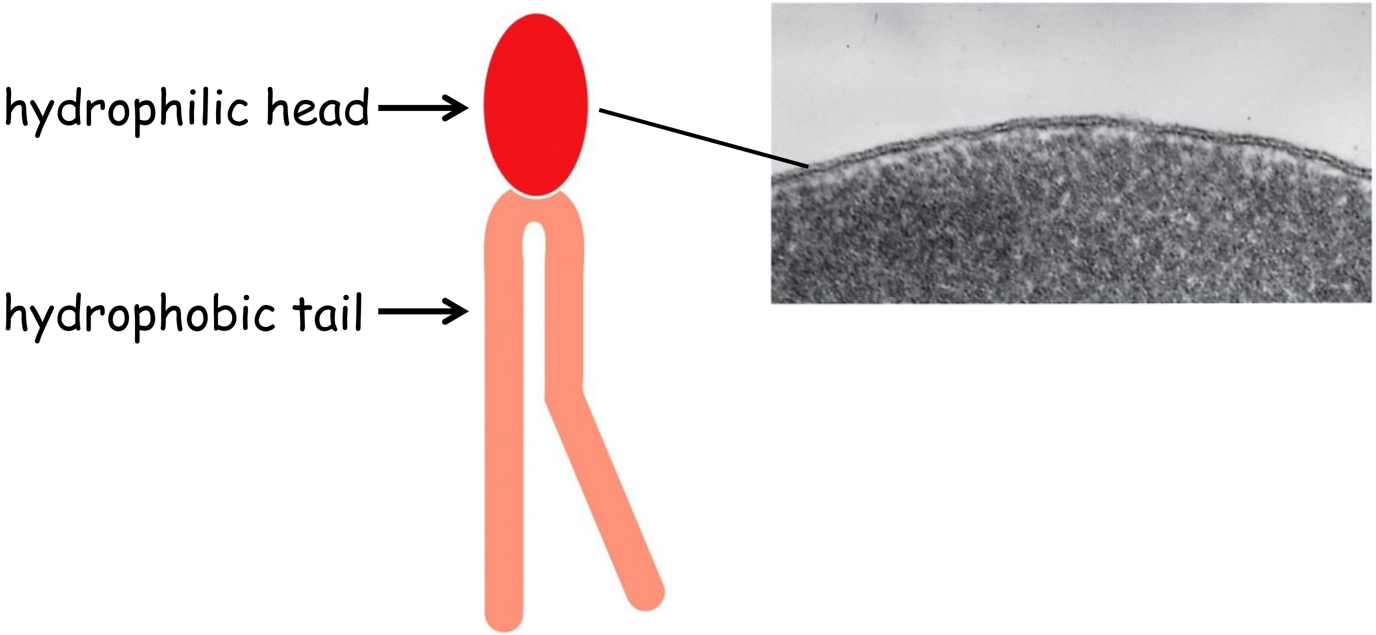
The plasma membrane is visible by electron microscopy.



The lipids in cell membranes combine two very different properties in a single molecule:

a hydrophilic (“water-loving”) head and
one or two hydrophobic (“water-hating”) hydrocarbon tails

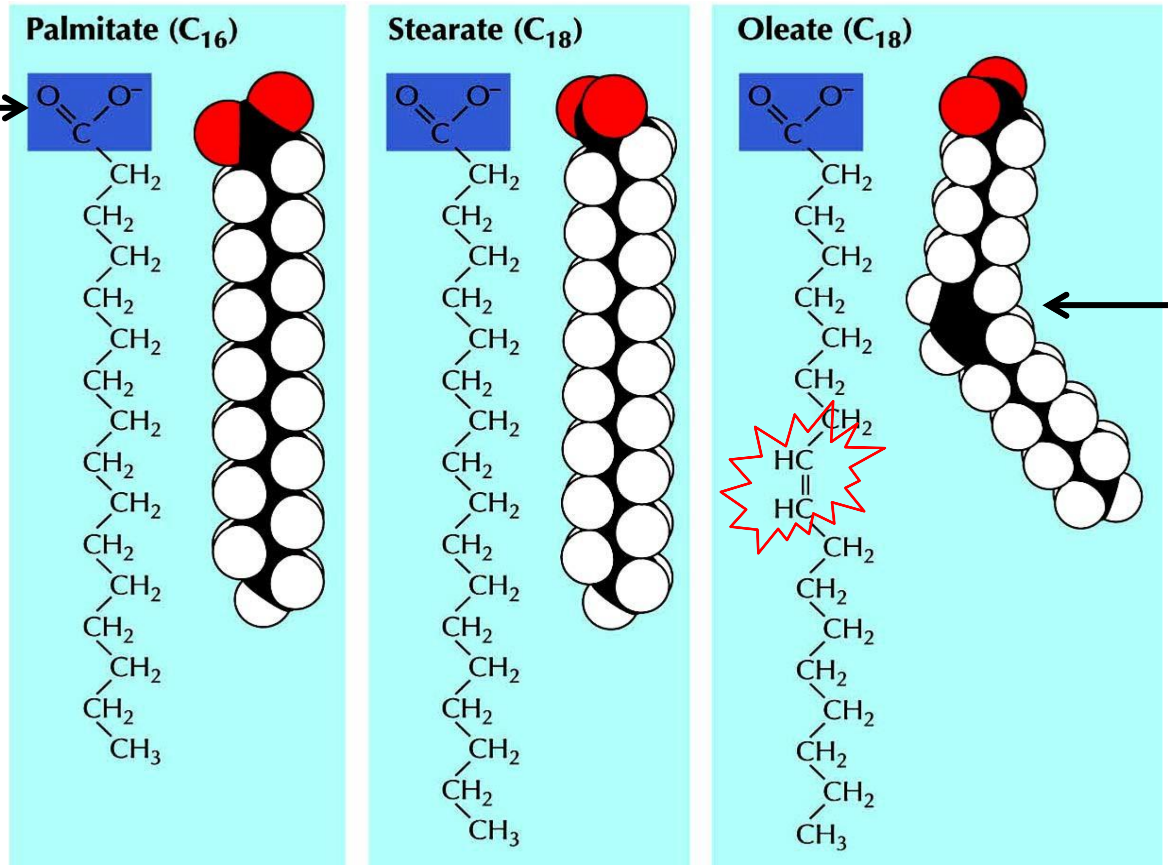
Molecules with both hydrophilic and hydrophobic properties are termed amphipathic



The simplest lipids: fatty acids

A fatty acid consists of a long hydrocarbon chain (16 to 18 carbon atoms) terminating in a carboxyl group at one end

negatively-charged carboxyl group



The double bond introduces a kink in the hydrocarbon chain

In saturated fatty acids all of the carbon atoms are bonded to the maximum number of hydrogen atoms (no double bonds between carbon atoms)

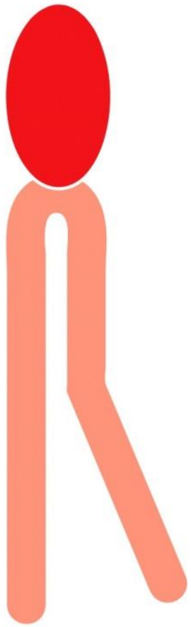
Unsaturated fatty acids contain one or more double bonds between carbon atoms

Chemical composition of membrane lipids

Three main types

1. **Phosphoglycerides** are diacylglycerides with small functional head groups linked to the glycerol backbone by phosphate ester bonds.
2. **Sphingolipids** are ceramides formed by the attachment of sphingosine to fatty acids.
3. **Cholesterol** is a smaller and less amphipathic lipid that is only found in animals.

The most abundant membrane lipids are the phospholipids: consist of two fatty acids linked to a polar head group.

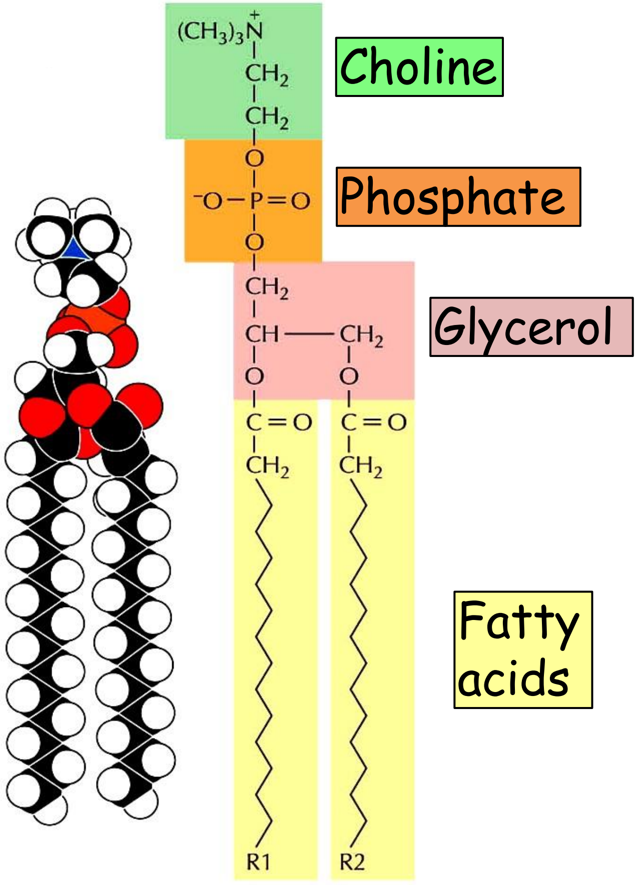


Usually mediated by the three-carbon molecule glycerol (phosphoglyceride): the two fatty acids are bound to carbon atoms in glycerol through ester linkages and the third carbon atom of glycerol is bound to a phosphate group (phosphatidic acid). The phosphate group is frequently attached to another small polar molecule, such as serine, choline, inositol and ethanolamine (e.g. phosphatidylserine).

Phosphatidylcholine

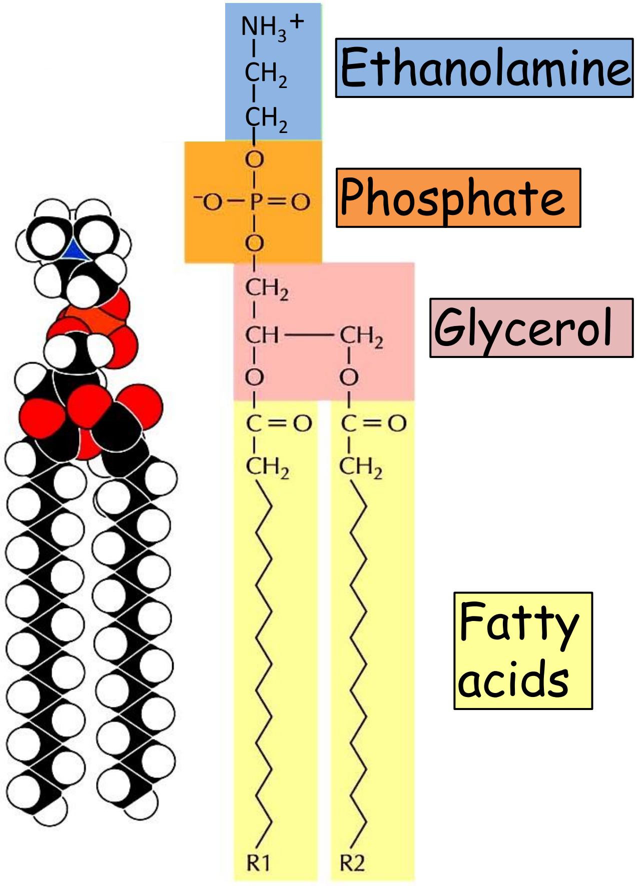
The most common type of phospholipid in most cell membranes is phosphatidylcholine.

The net charge of the polar head = (+1) + (-1) = 0



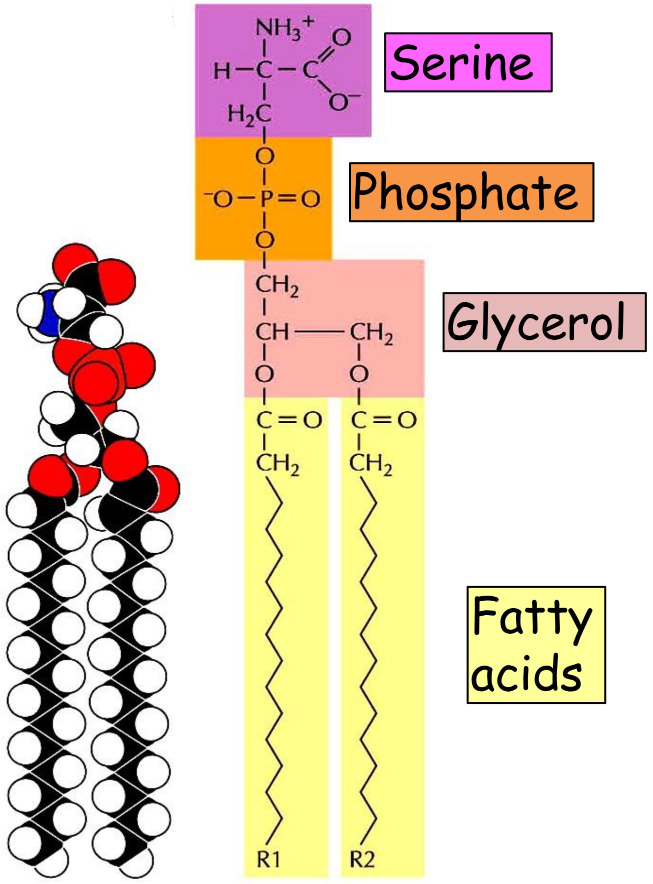
Phosphatidylethanolamine

The net charge of the polar head
= (+1) + (-1) = 0



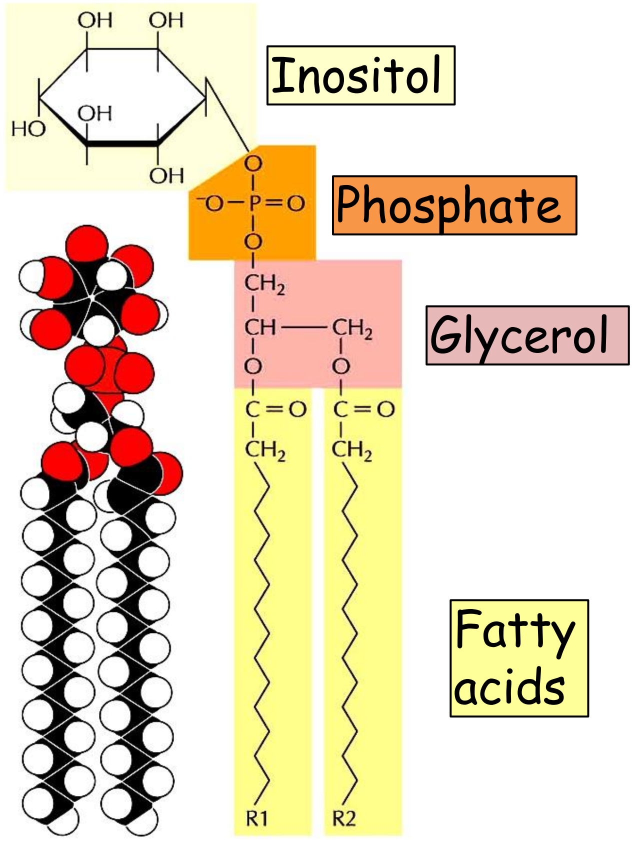
Phosphatidylserine

The net charge of the polar head
= (+1) + (-1) + (-1) = -1

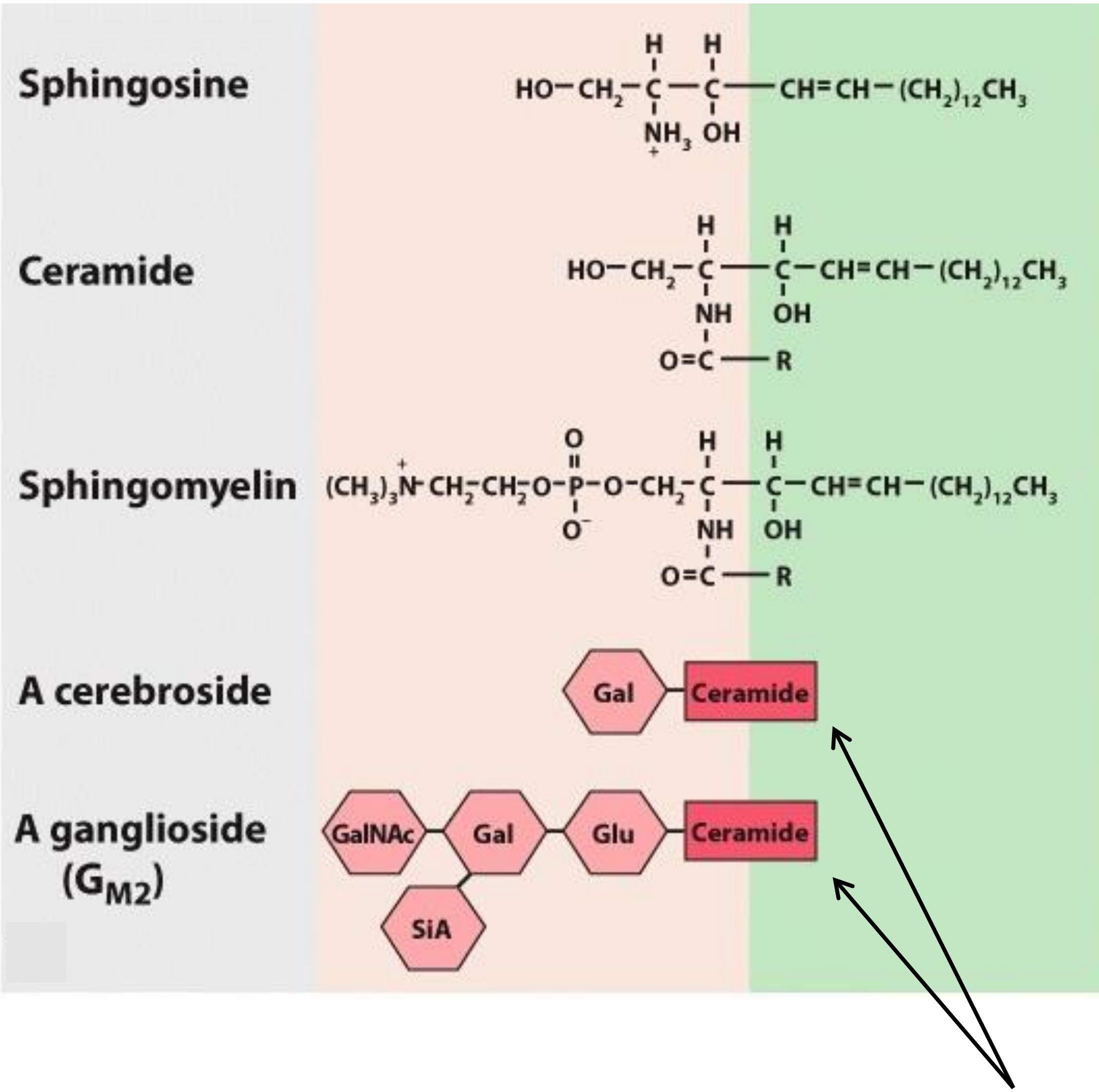


Phosphatidylinositol

The net charge of the polar head
= (0) + (-1) = -1



Sphingolipids



Sphingolipids are derived from sphingosine.

The addition of a second fatty acid to sphingosine through the amine group results in a lipid called ceramide.

The addition of phosphorylcholine to ceramide results in a lipid called sphingomyelin.

The addition of galactose to ceramide results in a lipid called a cerebroside.

The addition of complex carbohydrates including sialic acid to ceramide results in a lipid called a ganglioside.

The sugar-substituted lipids are called glycolipids.

These lipids are degraded in lysosomes. Recall from lecture on lysosomes:

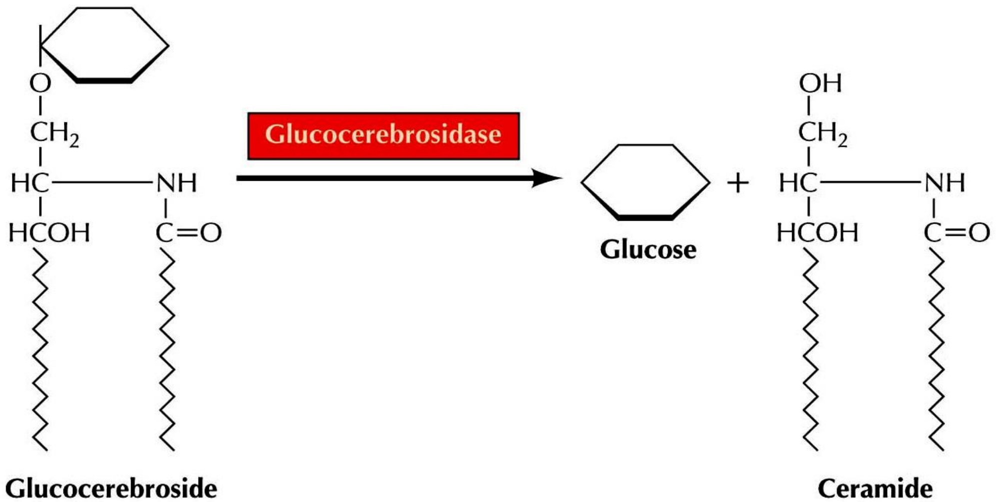
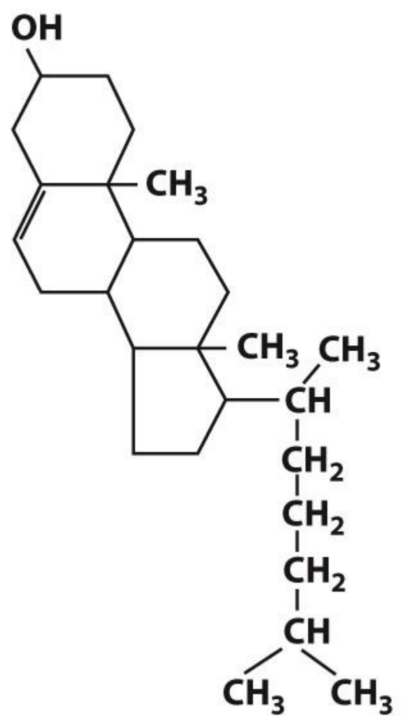
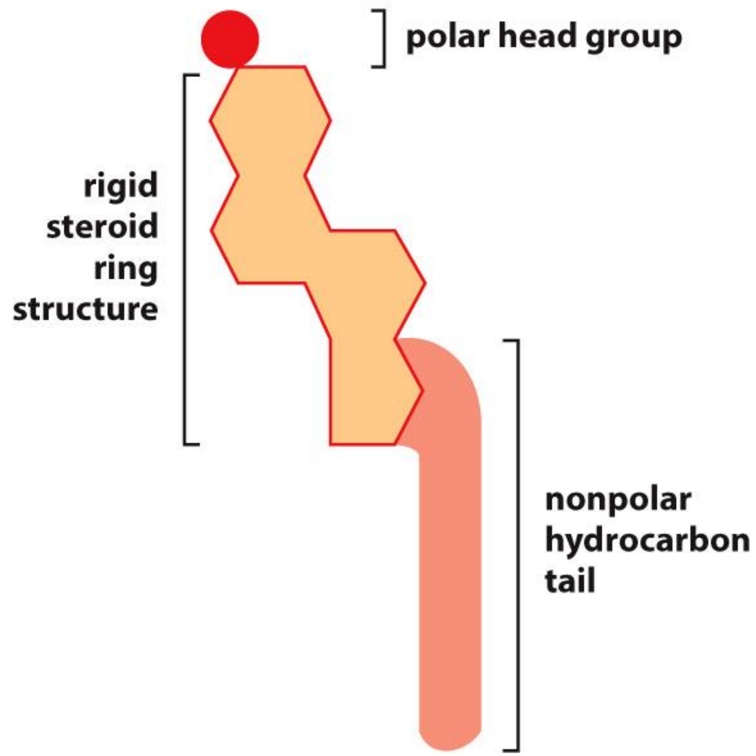


Table 1 ***Sphingolipid Storage Diseases***

Disease	Enzyme deficiency	Principal storage substance	Consequences
G_{M1} Gangliosidosis	G_{M1} β-Galactosidase	Ganglioside G_{M1}	Mental retardation, liver enlargement, skeletal involvement, death by age 2
Tay-Sachs disease	Hexosaminidase A	Ganglioside G_{M2}	Mental retardation, blindness, death by age 3
Fabry's disease	α-Galactosidase A	Trihexosylceramide	Skin rash, kidney failure, pain in lower extremities
Sandhoff's disease	Hexosaminidases A and B	Ganglioside G_{M2} and globoside	Similar to Tay-Sachs disease but more rapidly progressing
Gaucher's disease	Glucocerebrosidase	Glucocerebroside	Liver and spleen enlargement, erosion of long bones, mental retardation in infantile form only
Niemann-Pick disease	Sphingomyelinase	Sphingomyelin	Liver and spleen enlargement, mental retardation
Farber's lipogranulomatosis	Ceramidase	Ceramide	Painful and progressively deformed joints, skin nodules, death within a few years
Krabbe's disease	Galactocerebrosidase	Galactocerebroside	Loss of myelin, mental retardation, death by age 2
Sulfatide lipidosis	Arylsulfatase A	Sulfatide	Mental retardation, death in first decade

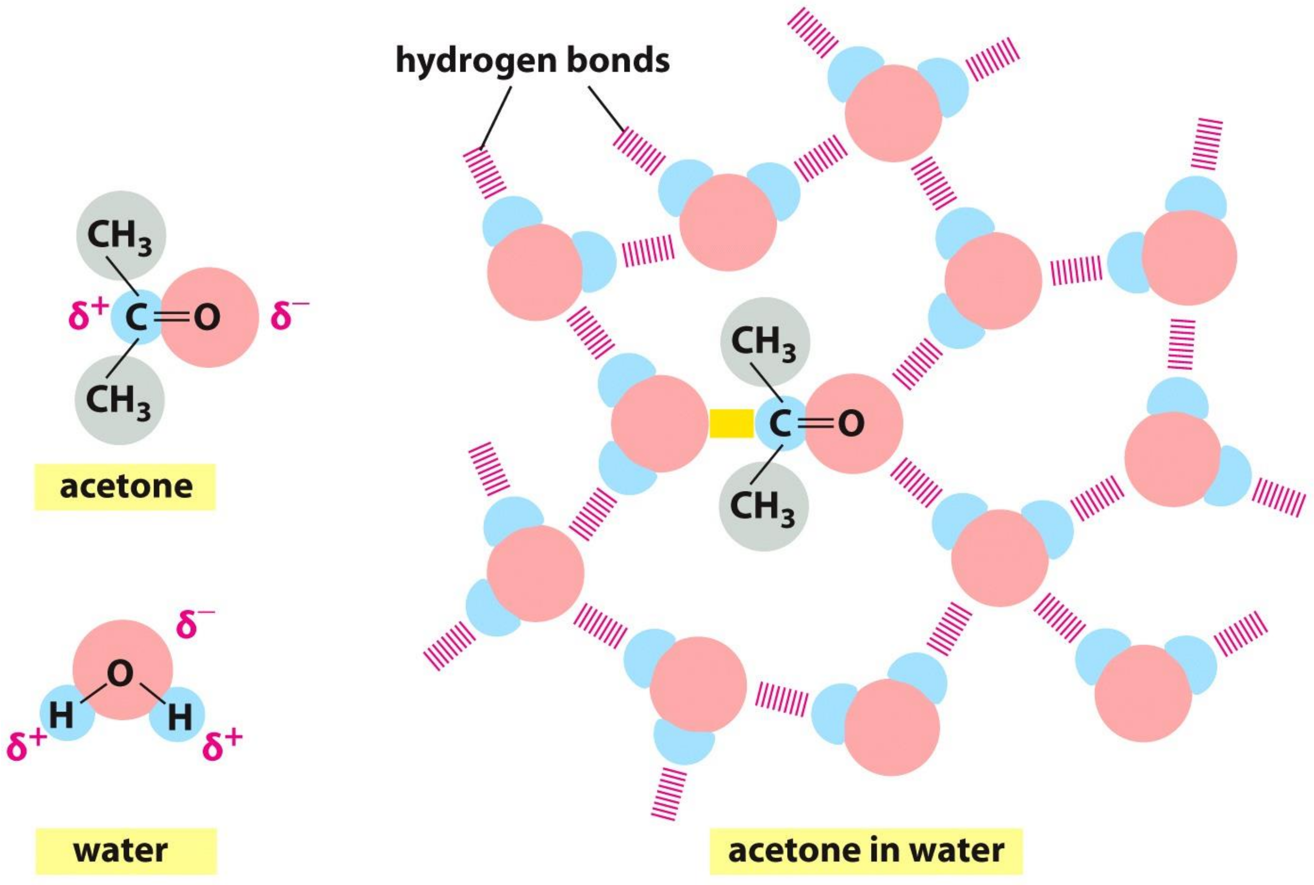
In addition to phosphoglycerides, sphingolipids and glycolipids, all cell membranes contain cholesterol



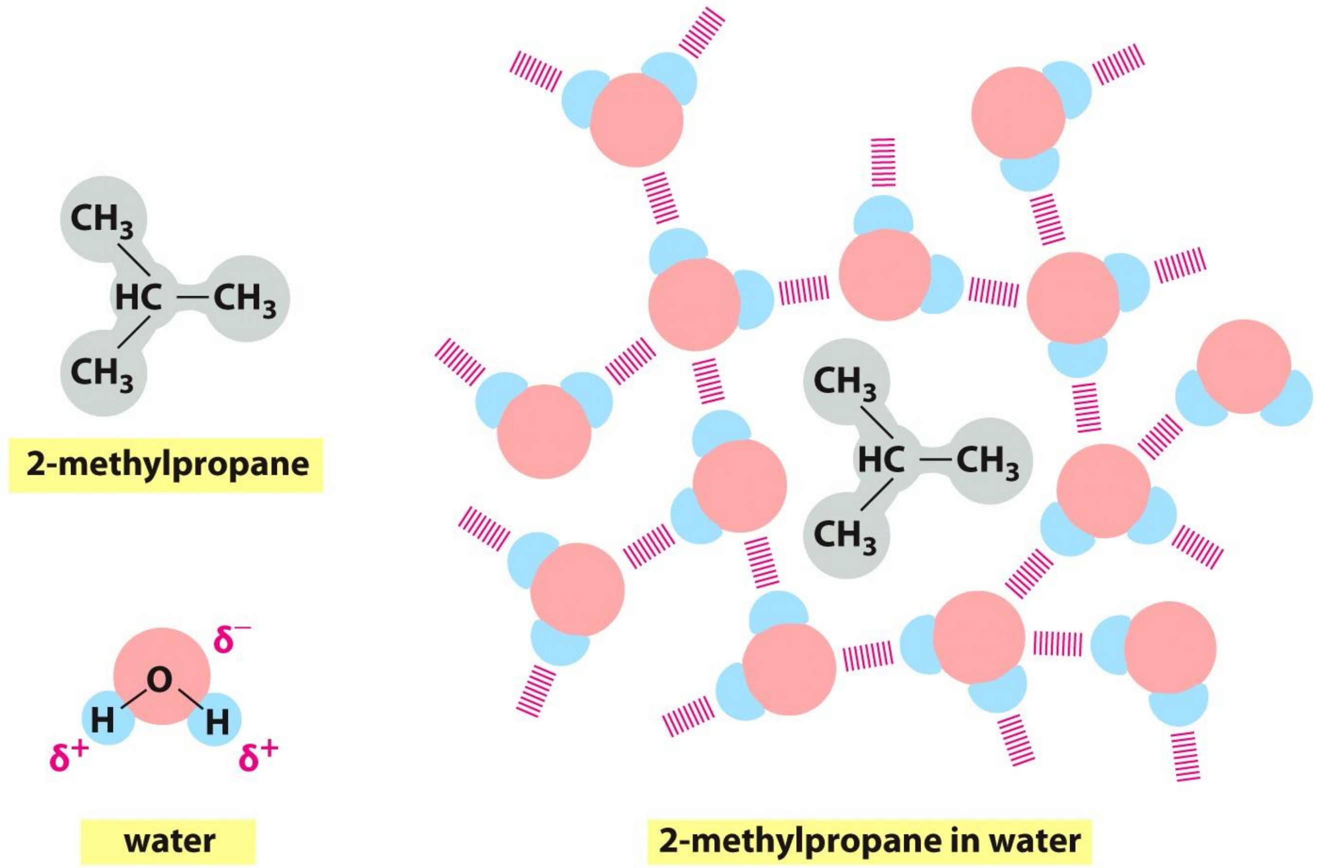


Cholesterol is amphipathic, with a hydrophilic head and one hydrophobic tail

Hydrophilic molecules dissolve in water because they contain charged atoms or polar groups and therefore can form electrostatic (hydrogen) bonds with water molecules.



Hydrophobic molecules are insoluble in water because all of their atoms are uncharged and nonpolar and therefore cannot form bonds with water molecules. The water forms a cage-like structure around the hydrophobic molecule.

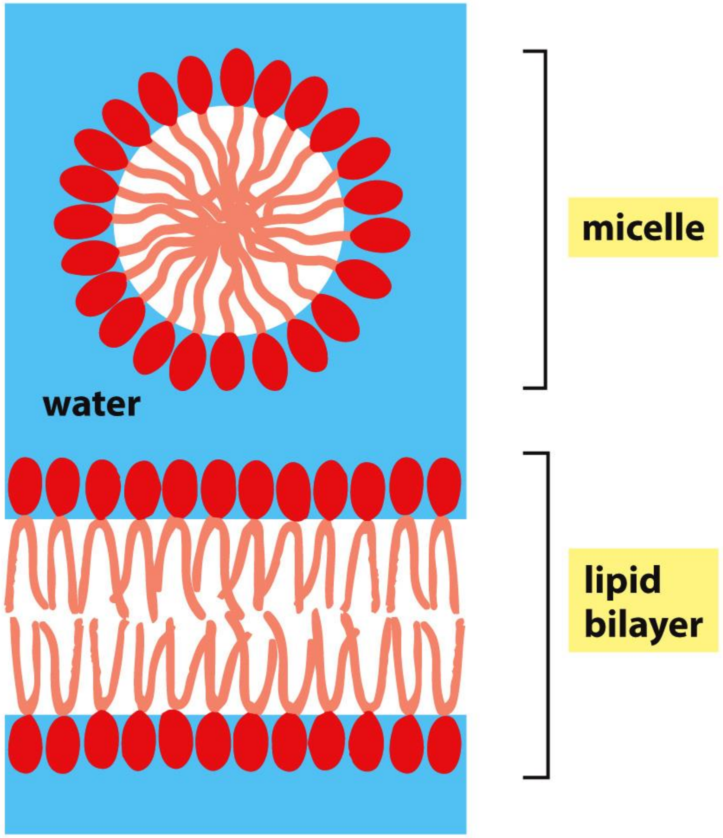


Why membranes form a bilayer

The formation of the cage structure of water molecules around the hydrophobic molecule requires energy.

The energy cost is minimized if the hydrophobic molecules cluster together (smaller number of water molecules are needed for the cage).

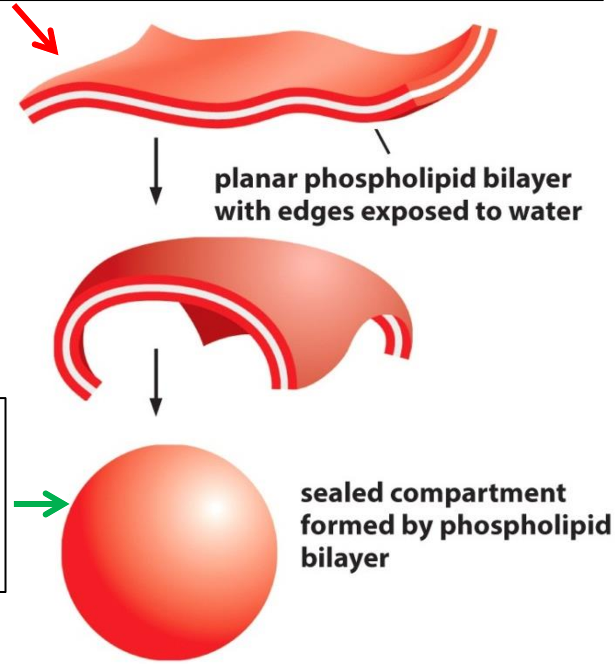
This is why, depending on the shape of the fatty acid tail, lipids can form micelles (tails inwards) or bilayers (tails sandwiched between the head groups).



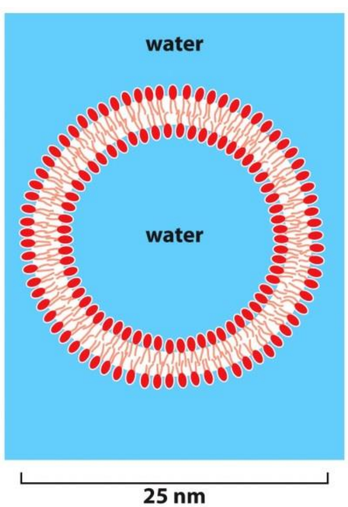
Why membranes naturally seal into enclosed structures

These same forces provide a bilayer with self-sealing properties. The exposed edges will rearrange spontaneously to the energetically more favourable state where they are not exposed to water.

energetically unfavourable



energetically favourable
Aqueous solution inside and outside.



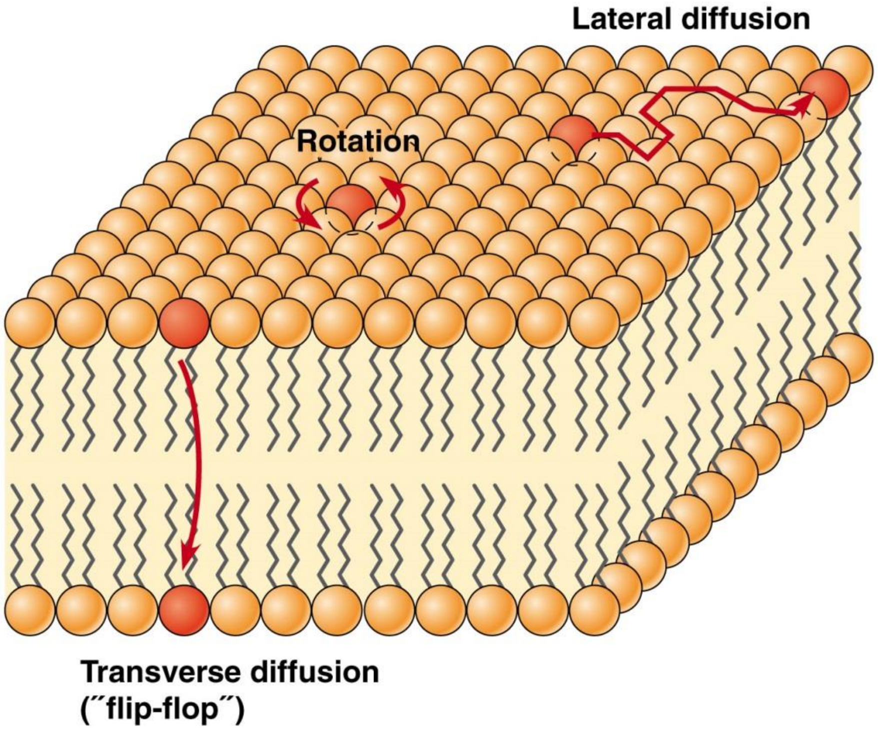
Pure phospholipids in water will spontaneously form **liposomes**

The lipid bilayer behaves as a two-dimensional fluid. Three types of lipid mobility account for this:

1. Lateral diffusion
2. Rotation
3. Flip-flop

1. Lateral diffusion – lipids rapidly exchange places with their neighbors (10^7 times per second). Gives rise to rapid diffusion (diffusion coefficient of 10^{-8} cm^2/sec) ⟹A lipid can move the length of a bacterial cell in 1 second.

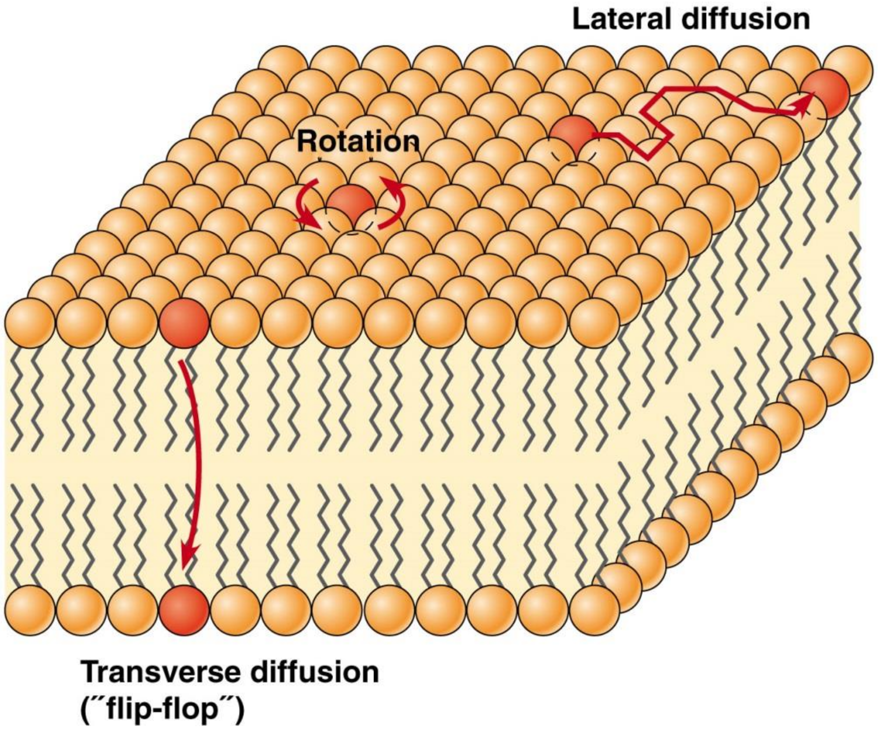
2. Rotation – lipids can rotate around their axis at speeds as high as 500 rpm.



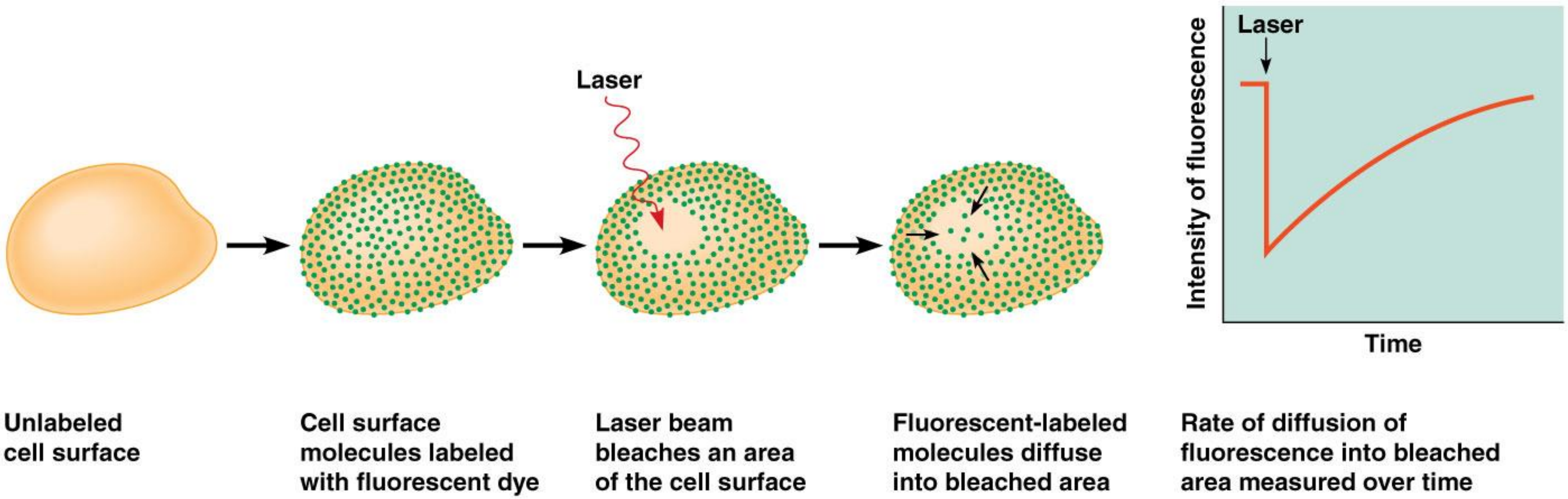
The lipid bilayer behaves as a two-dimensional fluid. Three types of lipid mobility account for this:

1. Lateral diffusion
2. Rotation
3. Flip-flop

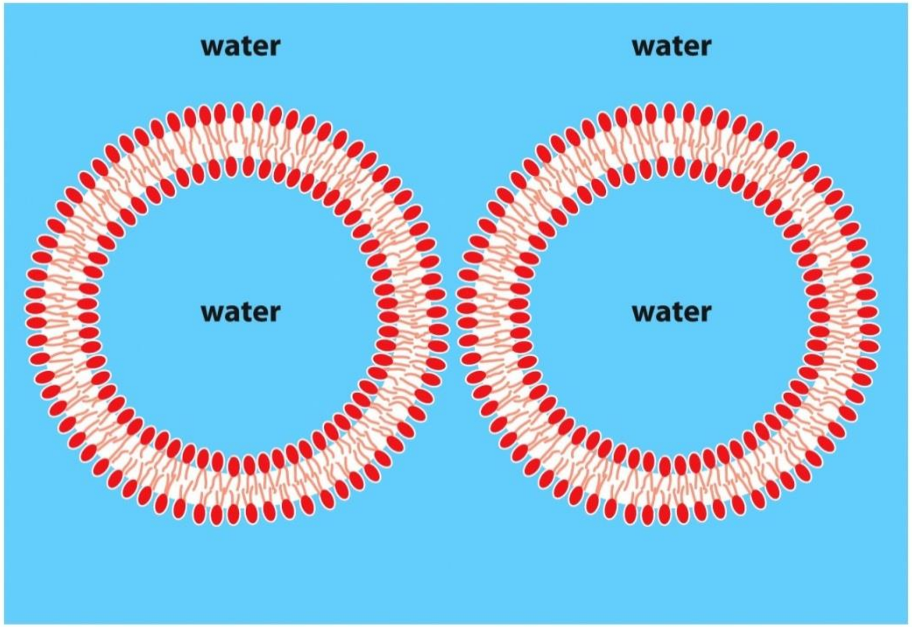
3. Flip-flop – rarely occurs, on the time scale of hours, assisted by enzymes called flippases. The exception is cholesterol which can flip rapidly on its own.



The fluid nature of membranes can be demonstrated by FRAP: fluorescence recovery after photobleaching



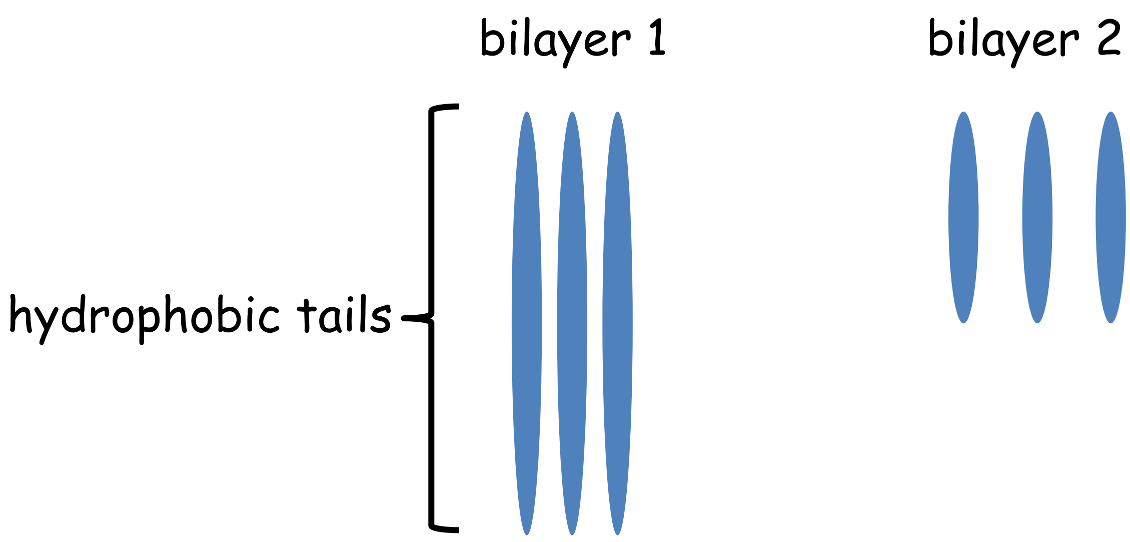
If bilayers are fluid, why do they not spontaneously fuse? The cage-like structure around the polar heads acts as an insulator and is not easily displaced. Membrane fusion requires many factors as well as energy. Thus, the hydration shell around the membrane contributes to keeping the organelles distinct and prevents uncontrolled fusion.



Membrane fluidity is also determined by the types of lipids

Two main properties of lipids contribute to fluidity: the length of the hydrocarbon tails and their degree of saturation (double bonds or not).

A shorter chain length reduces the tendency of the hydrocarbon tails to interact with one another and therefore increases the fluidity of the bilayer.

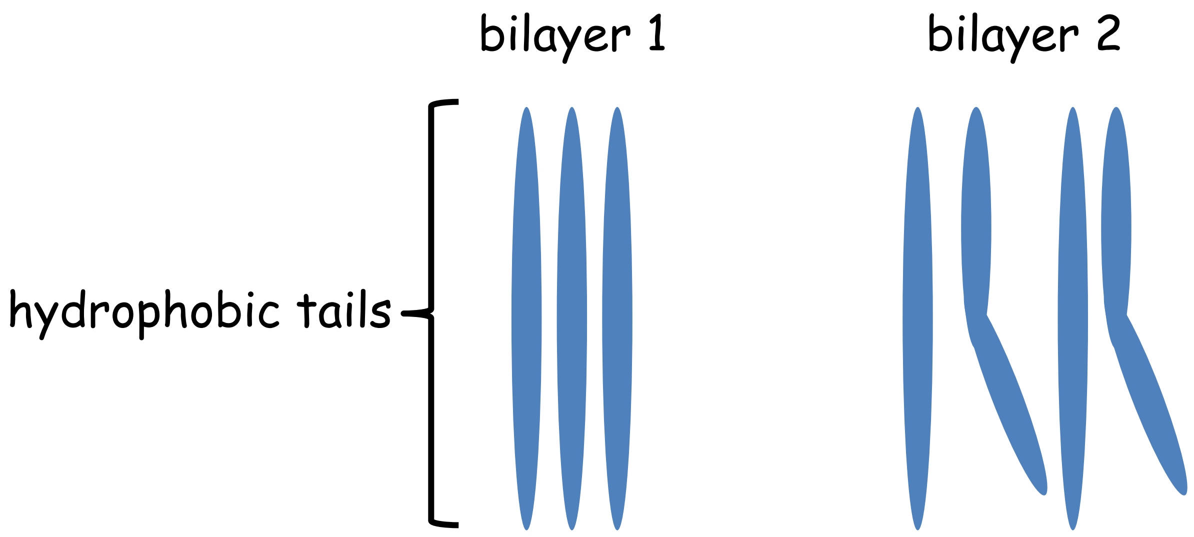


bilayer 2 is more fluid than bilayer 1

Membrane fluidity is also determined by the types of lipids

Two main properties of lipids contribute to fluidity: the length of the hydrocarbon tails and their degree of saturation (double bonds or not).

Unsaturated hydrocarbon tails introduce kinks into the chain, making them more difficult to pack together, increasing the fluidity of the bilayer. Such membranes are less viscous.

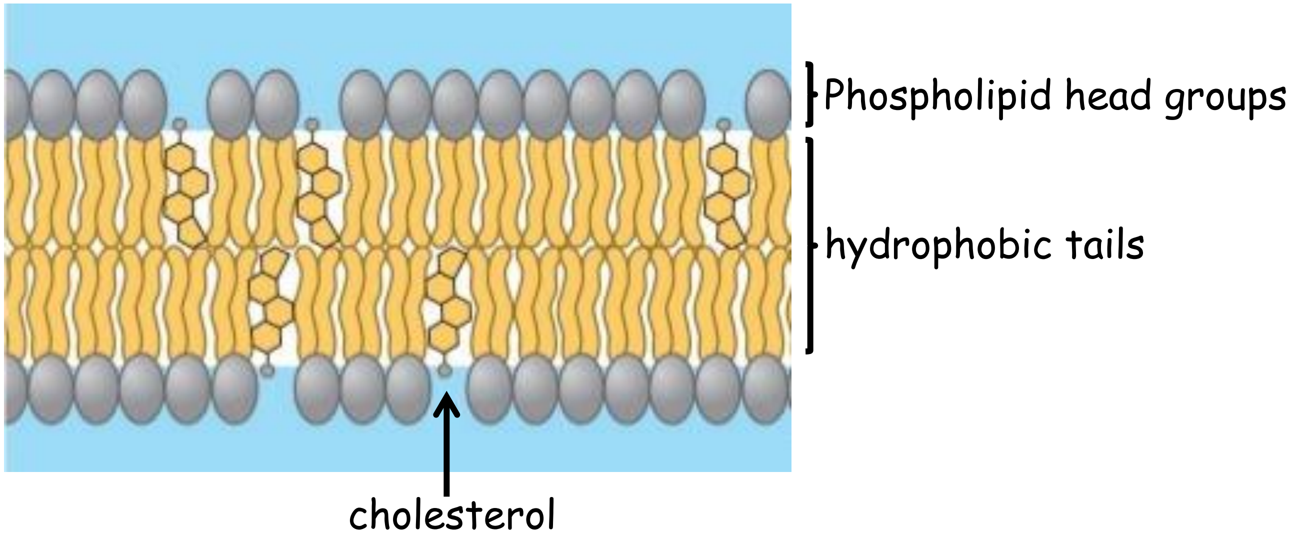


bilayer 2 is more fluid than bilayer 1

Cholesterol inserts into the membrane with its polar hydroxyl group close to the polar head groups of the phospholipids

The rigid hydrocarbon rings of cholesterol interact with, and partly immobilize, the regions of the fatty acid chains that are adjacent to the phospholipid head groups

Cholesterol makes the bilayer less fluid at high temperature, but keeps it fluid at low temperature.

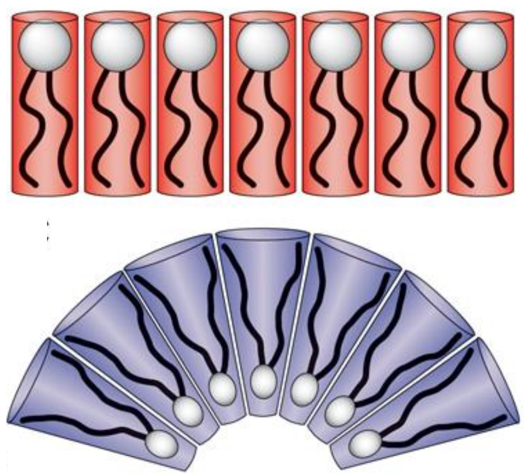


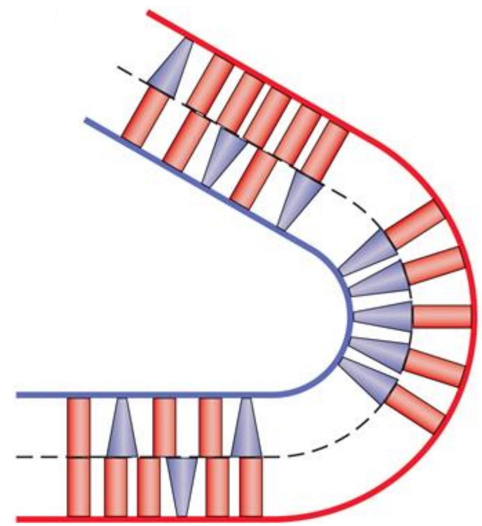
The lipid composition influences the properties of the membranes. Relatively small polar head groups (e.g. phosphatidylserine and phosphatidylethanolamine) give the lipid a "cone" structure. Those with larger head groups (phosphatidylcholine and phosphatidylethanolamine) give the lipid a cylindrical structure.

An abundance of conical lipids on the inner leaflet as opposed to the outer leaflet could allow for natural curvature of the membranes.

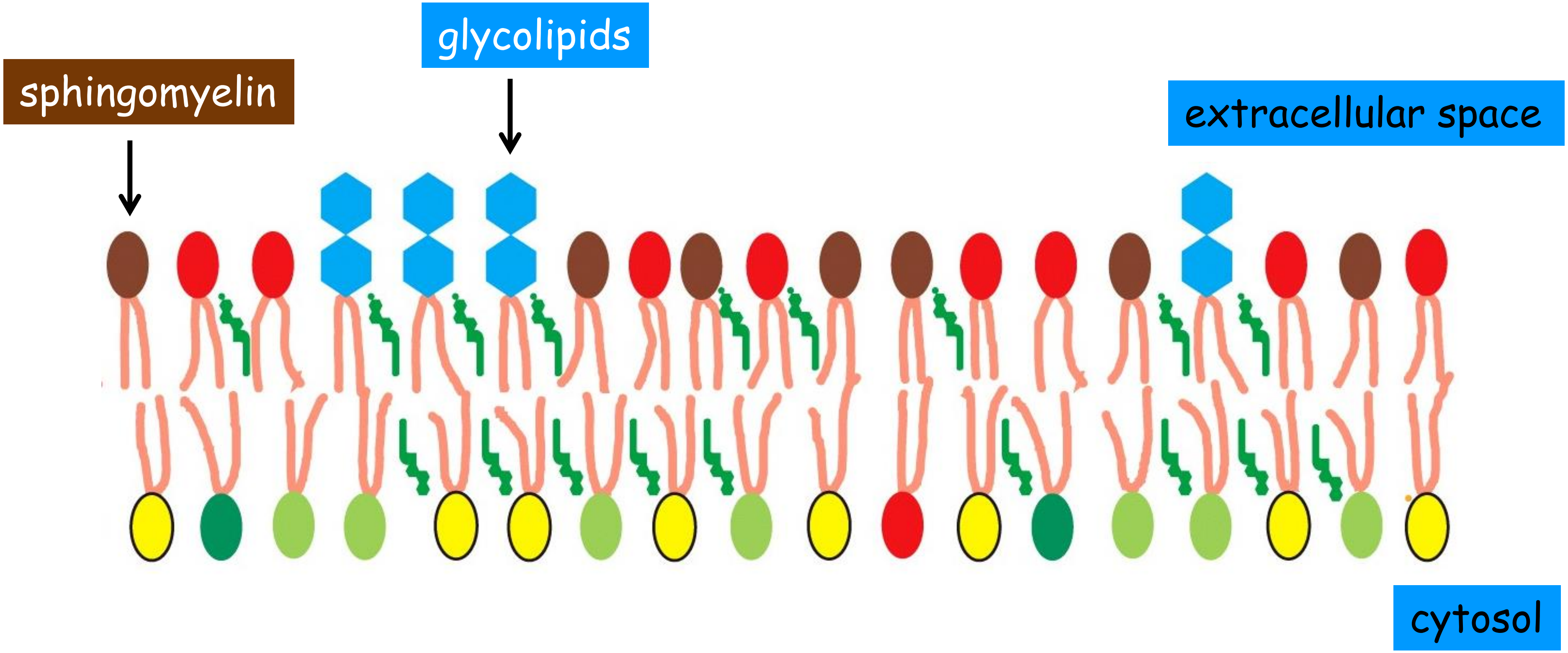
PC - cylindrical

PE - conical





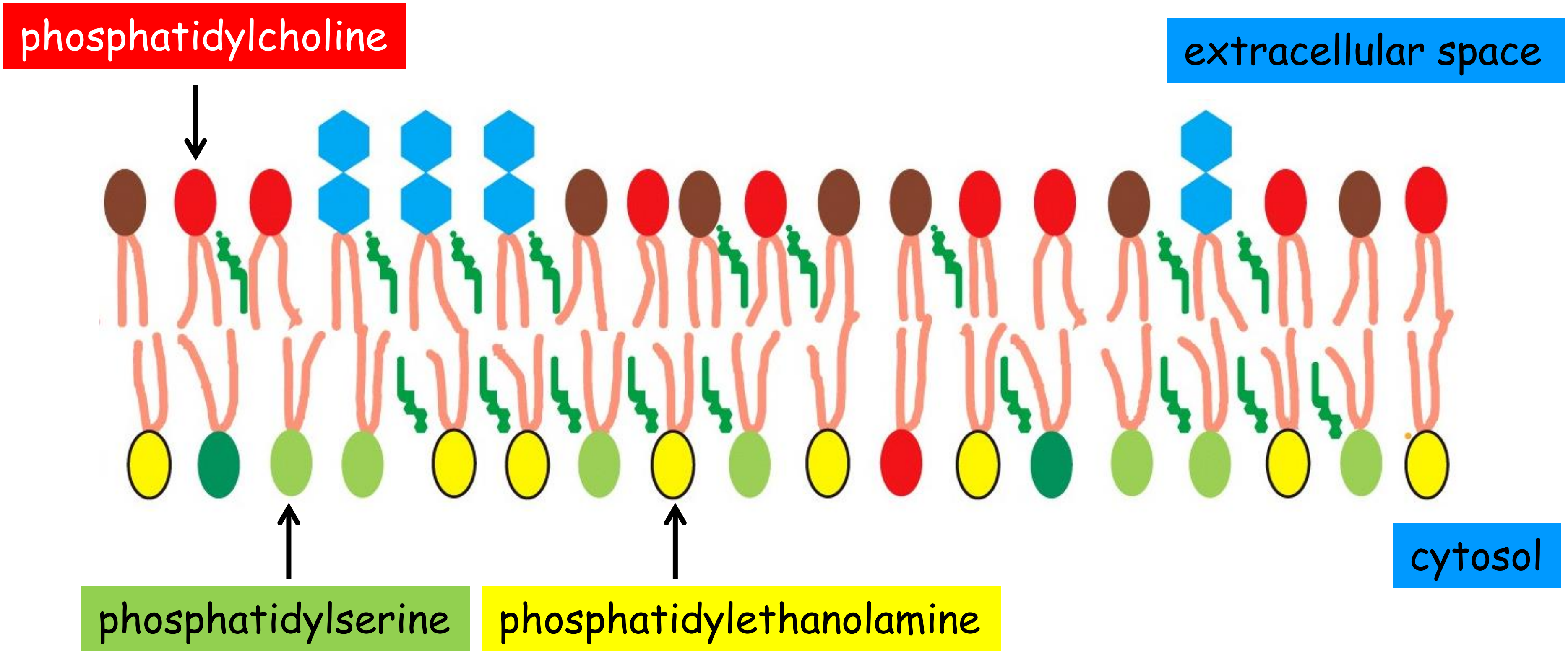
Asymmetric distribution of lipids in the plasma membrane



Glycolipids and sphingomyelin are only in the extracellular (outside) leaflet.

Both glycolipids and sphingomyelin are produced by enzymes exposed to the Golgi lumen and are not substrates for flippases.

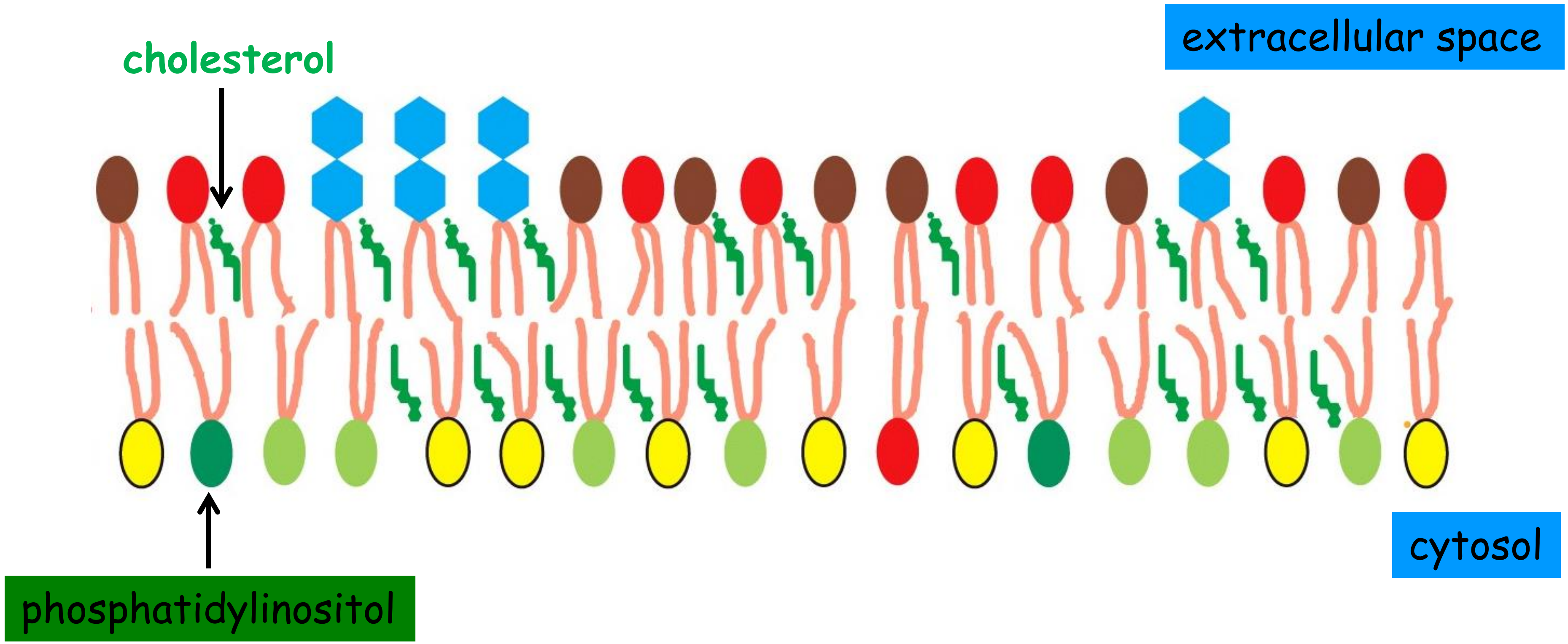
Asymmetric distribution of lipids in the plasma membrane



Phosphatidylcholine is mostly found in the outer leaflet.

Phosphoglycerides with terminal primary amine groups in the polar heads (phosphatidylserine and phosphatidylethanolamine) are maninly found in the inner leaflet. This asymmetry is due to the action of flippases.

Asymmetric distribution of lipids in the plasma membrane

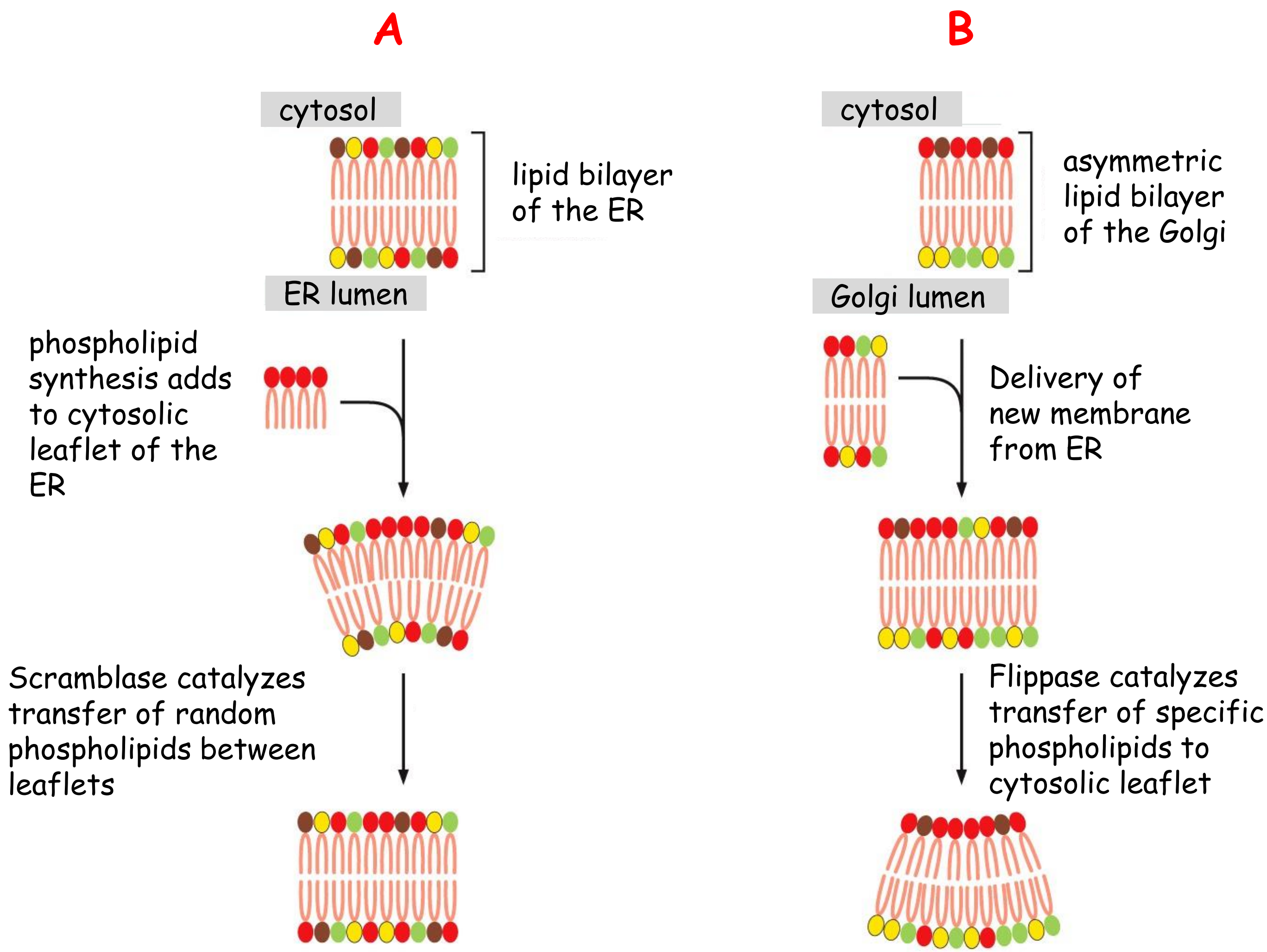


Phosphatidylinositols are minor constituents of the inner leaflet of the plasma membrane, with a role in cell signaling. This asymmetry is due to the action of flippases.

Cholesterol is evenly distributed between both leaflets and spontaneously shuttles between both leaflets without the need for flippases.

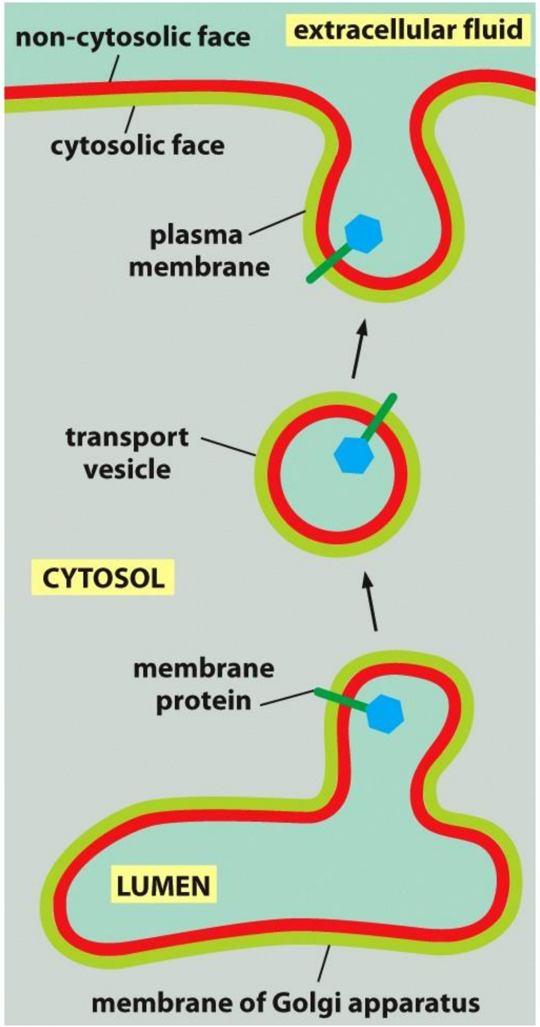
Phosphoglycerides are synthesized on the outer leaflet of the endoplasmic reticulum (A). An enzyme called scramblase randomly transfers the lipids to the inner leaflet, preventing buildup in the outer leaflet.

At the Golgi complex (B), flippases then distribute the lipids in a specific pattern.

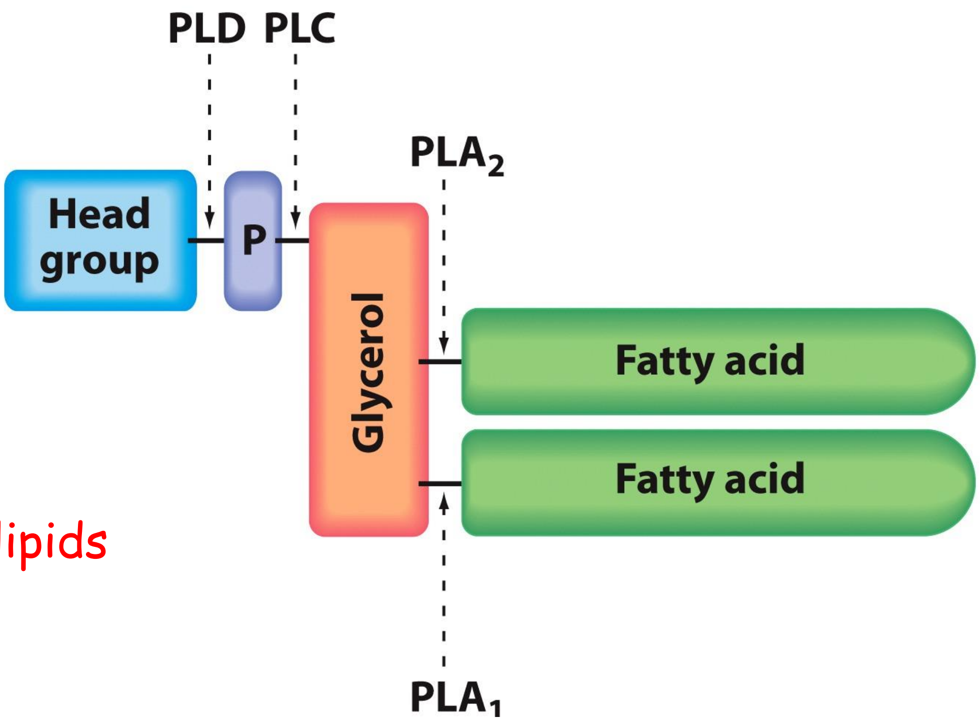


Membrane orientation does not change during transfer between compartments. Lipids facing the cytosol remain cytosolic even at the plasma membrane. Those facing the lumen of a compartment will face the extracellular space.

The same is true for proteins: those in the lumen of the organelle (or with parts in the lumen) will be released into the extracellular space, while the cytosolic portion remains facing the cytosol.



Phospholipids can be broken down at specific ester bonds by phospholipases. Phospholipase D releases the polar head group, phospholipase C releases the polar head group attached to the phosphate, and phospholipases A1 and A2 release the hydrophobic fatty acid chains from the C1 and C2 positions, repectively. Products produced by phospholipases are important signaling molecules.



PLD – generates phosphatidic acid
PLA1 and A2 – generate lysophospholipids